Title	An Active Surveillance, Post-Authorization Safety Study (PASS) to Estimate Incidence Rates of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among all Patients Treated with Ruxience for Rheumatoid Arthritis (RA) within the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA).
Protocol number	B3281011
Protocol version identifier	v.1
Date	14 October 2020
EU Post Authorisation Study (PAS) Register Number	TBD
Active substance	PF-05280586 Rituximab
Medicinal product	Ruxience (rituximab)
Product reference	H0004696
Procedure number	EMEA/H/C/004696/0000
Marketing Authorisation Holder (MAH)	Pfizer Europe MA EEIG
Joint PASS	No
Research question and objectives	**Research Question:** What are the incidence rates of safety events of special interest in patients with rheumatoid arthritis who are enrolled in the in the BSRBR-RA and initiate treatment with Ruxience?

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	Objectives: To estimate incidence rates of infections, including serious infections, malignancies, cardiovascular events, and events associated with use during pregnancy among patients with rheumatoid arthritis in the BSRBR-RA who initiate Ruxience.
Country(ies) of study	United Kingdom
Author	Cynthia de Luise, PhD, MPH Safety Surveillance Research, Worldwide Medical and Safety, Pfizer, Inc. 235 East 42nd Street, 219/08/01 New York, New York 10017 USA

Marketing Authorisation Holder(s)	*Pfizer Europe MA EEIG Boulevard de la Plaine 17, 1050 Bruxelles, Belgium*
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ACS	Acute coronary syndrome
ADA	Adalimumab
AE	adverse Event
BSRBR	British Society for Rheumatology Biologics Register
BSRBR-RA	British Society for Rheumatology Biologics Register Rheumatoid Arthritis
CI	confidence interval
CLL	Chronic lymphocytic leukaemia
csDMARD	Conventional Synthetic Disease Modifying Anti-rheumatic Drug
CV	cardiovascular
CVD	cardiovascular disease
DALYS	Daily-adjusted Life Years
DAS-28	Disease Activity Score 28
DMARD	disease modifying anti-rheumatic drug
EEIG	European Economic Interest Grouping
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ETA	etanercept
EU	European Union
GPA	Granulomatosis polyangiitis
HRQoL	Health-related Quality of Life
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
INF	infliximab
IRB	Institutional Review Board
MA	Market Authorisation
MACE	Major acute cardiovascular events
MAH	Market Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Microscopic polyangiitis
NHL	Non-Hodgkin's lymphoma
NI	Non-Interventional

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Abbreviation	Definition
NICE	National Institute for Health and Clinical Excellence
NMSC	non-melanoma skin cancer
NSAIDs	non-steroidal anti-inflammatory drugs
PAS	Post-Authorisation Study
PASS	Post-Authorization Safety Study
PV	Pemphigus Vulgaris
RA	Rheumatoid Arthritis
QALY	Quality-adjusted Life Year
RMP	Risk management plan
SAP	Statistical Analysis Plan
SMQ	Standarised MedDRA Queries
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
UK	United Kingdom

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3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Cynthia de Luise, PhD	Sr. Director, Safety Surveillance Research, Worldwide Medical and Safety	Pfizer, Inc.	235 East 42nd Street, 219/08/01 New York, New York 10017 USA
Kimme Hyrich, MD, PhD, FRCPC	Professor of Epidemiology and Consultant Rheumatologist	The University of Manchester	Centre for Musculoskeletal Research, 2nd Floor Stopford Bldg, Oxford Road, Manchester M13 9PL United Kingdom

Country Coordinating Investigators

Not applicable.

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4. ABSTRACT

Title: An Active Surveillance, Post-Authorisation Safety Study (PASS) to Estimate Incidence Rates of Safety Events of Special Interest among all Patients Treated with Ruxience for Rheumatoid Arthritis (RA) within the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA).

Version: 1

Date: 14 October 2020

Main Author: Cynthia de Luise, PhD, MPH, Pfizer, Inc.

Rationale and Background:
Rituximab is a genetically engineered chimeric mouse/human monoclonal IgG1k antibody targeting the transmembrane CD20 antigen. CD20 is a 32-kDa, non-glycosylated transmembrane phosphoprotein, located on the surface of normal precursor-B cells, mature B lymphocytes and malignant B cells. The natural ligand for CD20 has not been identified, and the biological function of CD20 remains unclear. Rituximab binds to a discontinuous conformational epitope on CD20 and initiates multiple immune effector functions leading to target cell lysis. The currently approved indications for licensed rituximab (MabThera) are for Rheumatoid arthritis (RA), Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukaemia (CLL), Granulomatosis with polyangiitis (GPA), Microscopic polyangiitis (MPA) and Pemphigus Vulgaris (PV).[1]

Licensed as MabThera in the European Union (EU) in 1998, rituximab was the first biologic on the market for RA for specific B cell targeting therapy. Rituximab in combination with methotrexate is indicated for the treatment of adult patients with severe active RA who have had an inadequate response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies. Approved in the EU on 1 April 2020, PF-05280586 (Ruxience) has been developed by Pfizer as a biosimilar to the licensed reference product, MabThera. Pfizer proposes the assessment of safety events of special interest based on the Ruxience Risk Management Plan (RMP) v. 1.0 (infections including serious infections (Important Identified Risk), malignancies (Important Potential Risk), impact on cardiovascular disease (CVD) (Important Potential Risk) and use in pregnancy (Missing Information).[2] This protocol describes a post-authorisation safety study (PASS) of Ruxience-exposed patients using actively collected prospective data included in the established BSRBR-RA. This study is designated as a Category 4 "Additional Pharmacovigilance Activities" in line with the reference product.

Research Question: What are the incidence rates of safety events of special interest in patients with rheumatoid arthritis who are enrolled in the in the BSRBR-RA and initiate treatment with Ruxience?

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Objectives: To estimate incidence rates of infections, including serious infections, malignancies, cardiovascular events, and events associated with use during pregnancy among patients with rheumatoid arthritis in the BSRBR-RA who initiate Ruxience.

Study Design: This is an active surveillance study using existing data within the BSRBR-RA, an ongoing, prospective, observational cohort study started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post-marketed clinical use.

Population: The study population will comprise all patients with RA enrolled within the BSRBR-RA who initiate treatment with Ruxience.

Data Sources: The BSRBR-RA was established in 2001 to study the safety of biologic therapies in RA patients living in the United Kingdom (UK).

Variables: This study will focus on specific variables routinely captured in the BSRBR-RA and include baseline patient characteristics (ie, clinical and demographic characteristics, comorbidities and current and past therapies), and safety events of special interest including serious infections, malignancies, CV events, and events associated with use during pregnancy.

Study Size: This is a descriptive study without pre-specified hypotheses, therefore there is no minimum sample size requirement. All Ruxience-treated patients with data in the BSRBR-RA during the study period will be included in this study.

Study Period: The Study Start Date is defined as the date when the first patient entered in the BSRBR-RA with RA initiates Ruxience. The Study End Date is defined as 3 years after the Study Start Date.

Data Analysis: Annual reports will consist of descriptive summaries of uptake of patients exposed to Ruxience and baseline variables. The final report will consist of incidence rates of safety events of interest described above for Ruxience-treated patients. No comparative analyses with other cohorts will be performed.

Milestones: The first annual report describing the number and characteristics of patients initiating Ruxience is estimated by 31 July 2021 and annually thereafter through 31 July 2023. A final report estimating incidence rates of events of special interest is expected by 31 December 2023.

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5. AMENDMENTS AND UPDATES

None.

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6. MILESTONES

Deliverable	Estimated Timeline
Registration in the EU PAS Register	TBD
Start of data collection (estimated)	31-May-2021^
Date of first annual report (estimated)	31-July-2021
Date of second annual report (estimated)	31-July-2022
Date of third annual report (estimated)	31-July-2023
End of data collection (estimated)	31-July-2023#
Final report (estimated)	31 December 2023x

^ Start of data collection is the planned date for starting data extraction for the purposes of the first annual report.

End of data collection is the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).

x Final report must be prepared within 11 months of end of data collection.

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7. RATIONALE AND BACKGROUND

RA is a chronic and systemic inflammatory disease with an estimated prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05% within Northern European and North American populations.[3] RA is characterised by inflammation, joint destruction, and progressive disability. Joint destruction is frequently irreversible resulting in significant cumulative morbidity. Patients experience a broad range of co-morbidities.[4] Compared with the general population, RA patients are at a higher risk of infections, CV disease (CVD) and malignancies (including lymphoma).[5,6,7,8,9,10,11,12,13] These patients are also treated with multiple classes of agents, including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and DMARDs including biologicals, each of which carry significant risks as well as benefits.

Rituximab is a genetically engineered chimeric mouse/human monoclonal IgG1k antibody targeting the transmembrane CD20 antigen. CD20 is a 32-kDa, non-glycosylated transmembrane phosphoprotein, located on the surface of normal precursor-B cells, mature B lymphocytes and malignant B cells. The natural ligand for CD20 has not been identified, and the biological function of CD20 remains unclear. Rituximab binds to a discontinuous conformational epitope on CD20 and initiates multiple immune effector functions leading to target cell lysis. The currently approved indications for licensed rituximab (MabThera) are for Rheumatoid arthritis (RA), Non-Hodgkin's lymphoma (NHL), Chronic lymphocytic leukaemia (CLL), Granulomatosis with polyangiitis (GPA), Microscopic polyangiitis (MPA) and Pemphigus Vulgaris (PV).[2]

Licensed as MabThera in the European Union (EU) in 1998, rituximab was the first biologic on the market for RA for specific B cell targeting therapy.[14] Rituximab in combination with methotrexate is indicated for the treatment of adult patients with severe active RA who have had an inadequate response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs) including one or more tumour necrosis factor (TNF) inhibitor therapies.

Biosimilars and non-originator biologicals of rituximab have been approved in several additional countries as of July 2018, including Turkey, Russia, Argentina, South Korea, Australia, and India.[15] The EMA approved two rituximab biosimilars from 2 MAHs including Rixathon (Sandoz) in June 2017, and Truxima (Celltrion) in November 2018. PF-05280586 (Ruxience) has been developed by Pfizer as a proposed biosimilar to the licensed reference product MabThera and was approved on 1 April 2020.

The Market Authorisation Holder (MAH) proposes the assessment of safety events of special interest based on the Ruxience RMP v. 1.0 (infections including serious infections (Important Identified Risk), malignancies (Important Potential Risk), impact on cardiovascular disease (CVD) (Important Potential Risk) and use in pregnancy (Missing Information).[2]

This study is designed as a Post-authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer. This study is designated as "Category 4 Additional Pharmacovigilance Activities" in line with the reference product.

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8. RESEARCH QUESTION AND OBJECTIVES

What are incidence rates of safety events of special interest in patients with RA who initiate treatment with Ruxience and are enrolled in the BSRBR-RA?

9. RESEARCH METHODS

To estimate incidence rates of infection, including serious infections, malignancies, cardiovascular (CV) events and events associated with use during pregnancy among all patients with RA in the BSRBR-RA who initiate treatment with Ruxience.

9.1. Study Design

This is an active surveillance study using existing data within the BSRBR-RA, an ongoing, prospective, observational cohort study started in 2001 with the primary aim of studying the safety of new therapies for RA during routine post-marketed clinical use.

9.2. Setting

The BSRBR-RA was established in 2001 to study the safety of biologic therapies in RA patients living in the UK. For the first 7-8 years the main focus was on the study of the safety profile of the first three tumor necrosis factor inhibitor (TNFi) agents (ie, adalimumab (ADA), etanercept (ETA) and infliximab (INF) as a class and as individual therapies. At the time the register was established, the most appropriate comparison group for these three TNFi agents was patients with active RA receiving treatment with csDMARDs. The register remains a relevant resource for studying the safety profile of new biologic, biosimilar and other targeted therapies as they receive National Institute for Health and Clinical Excellence (NICE) approval and are used in real world practice where patients have more diverse clinical background and comorbidities than a typical clinical trial population.

Unique features of BSRBR-RA include recruitment and collection of data from parallel comparison groups of patients consisting of (i) those with active RA who were treated with csDMARDs, and (ii) those with active RA who are biologic naïve treated with TNFi, a high proportion of recruited patients in the UK (>80%), and linkage with national mortality and malignancy registries.[16] Several studies have been conducted using data from the BSRBR-RA including work regarding risks of infections,[17] and malignancies.[18,11] All patients within the BSRBR-RA provided informed and signed consent for participation (Study Reference 00/8/053).

External validity, ie, generalisability to RA patients who are not enrolled in the register, is maximised by encouraging physicians to enrol each and every patient meeting inclusion criteria, regardless of their baseline demographic or clinical characteristics or treatment history.

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9.2.1. Inclusion Criteria

1. Eligible for inclusion in BSRBR-RA;
2. Newly initiated treatment with Ruxience for RA;
3. Age >16 years at the initiation of Ruxience treatment.

9.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

9.3. Variables

This study will focus on specific variables routinely captured in the BSRBR-RA and include baseline patient characteristics (ie, clinical and demographic characteristics, comorbidities and current and past therapies), and safety events of special interest including serious infections, malignancies, CV events, and events associated with use during pregnancy.

9.3.1. Baseline Data

Baseline data are derived from BSRBR-RA reported by the recruiting clinician (or patient where noted), using a standardised form:

1. Diagnosis (including the presence or absence of those features listed in 1987 American College of Rheumatology (ACR) criteria for RA);
2. Age at treatment start, gender, year of recalled symptom onset, year of diagnosis;
3. Ethnicity (patient form);
4. Previous drug history of immunosuppressive csDMARDs and biologics, biosimilar or other new advanced therapy, including duration of therapy recorded as start month/year;
5. Comorbidity (ie, http://bsrbr.org/hospitals/data collection/);
6. All current therapy for all illnesses.

9.3.2. Endpoints

The BSRBR-RA is an existing, efficient data collection system for evaluating a range of safety outcomes associated with therapies used to treat RA including cancers,[11,18] cardiovascular events[19] and serious infections.[17] The endpoints collected in BSRBR-RA are events associated with RA itself and therapies used to treat moderate to severe disease. The following events of interest have been pre specified for this study.

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1. Hospitalised infections overall.

2. NMSC.

3. Cardiac disorders: including but not limited to heart failure, coronary artery disease, myocardial infarction, and other cardiac disorders.

4. Malignancies, excluding NMSC.

5. Events associated with use during pregnancy.

9.4. Data Sources

BSRBR is the source of core baseline data, including patient demographics and disease characteristics collected by the recruiting clinician, using a standardised form.

Follow up
BSRBR data are the source of information on anti-rheumatic treatment, updated every 6-12 months depending on how long a patient has been in the register (6 monthly for the first 3 years and 12 monthly thereafter). This change is to reduce the burden of data capture on study sites, but the same data are collected at each follow-up. As many patients starting Ruxience will have been enrolled previously when they started Mabthera, follow-up may only be every 12 months. Some patients starting Ruxience as their first anti-B cell therapy will provide data more often as per the BSRBR protocol and some trusts may decide themselves to reconsent patients each time they switch drugs and send data every 6 months for 3 years again. Data captured includes continuation on drug and dates and reasons for stopping, with details of any change in dose and commencement of any new co therapy. Clinical information to permit calculation of the Disease Activity Score in 28 joints (DAS-28) is also collected.

Endpoints
BSRBR data include reports of serious morbidity reported directly by the rheumatology team at each scheduled follow-up date. For serious events additional data are captured, either against a pre-specified set of questions for certain events of special interest or using an open request for additional data. All events included in this protocol are considered events of special interest. All serious morbidities reported to BSRBR are coded by a trained nurse using the Medical Dictionary for Regulatory Activities (MedDRA).

BSRBR is linked to the UK national death and cancer registers which allow the “flagging” of individuals such that if they die or are entered in a cancer register, the BSRBR-RA learns of the event and obtains death certificate details or cancer register details. These data are held in a separate secure data safe haven at the University of Manchester. On average deaths are usually reported within 1 week to the national register although cancers can take much longer due to the structure of national reporting. BSRBR-RA received a download of death and cancer on average once/year.

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9.5. Study Size

This is a descriptive study without pre-specified hypotheses, therefore there is no minimum sample size requirement. All Ruxience-treated patients with data in the BSRBR-RA during the study period will be included in this study. Table 1 displays precision estimates for reported incidence proportions of safety events in Ruxience RMP.

Table 1. Precision Estimates for Reported Incidence Proportions of Safety Events in Ruxience RMP[2]

Condition	Incident Count	Population at Risk	Incidence Proportion	Lower Bound of 95% CI	Upper Bound of 95% CI
Any infection (including serious infection)	22	73	0.301	0.199	0.420
Serious infection	3	73	0.041	0.009	0.115
Malignancy (excluding NMSC)	1	73	0.014	0.000	0.074
NMSC	0	73	0.000	0.000	0.049
CV events	3	73	0.041	0.009	0.115
Events during pregnancy	0	73	0.000	0.000	0.049

NMSC, non-melanoma skin cancer; CV, cardiovascular; CI, confidence interval.

9.6. Data Management

All data are submitted by the local hospital sites to the University of Manchester via a secure online web portal. The BSRBR-RA data capture system is a web-based (https://bsrbr.org/database/), access managed, secure system hosted on the University of Manchester virtual secure servers which is accessed by 160 NHS clinical sites across the UK. NHS clinical staff use the web interface to log into their restricted area, enter and submit clinical data and efficiently communicate with study staff. The system uses encryption in transit and at rest and secure web authentication. Further details are provided here.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

All statistical analyses will be performed by BSRBR using Stata. The annual analyses will include all patients who have received Ruxience (baseline characteristics) and event incidence reports will include all patients with study follow-up data.

Analyses will be undertaken at 12 monthly intervals and will include recruitment details, baseline characteristics and crude event rates.

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The final analysis will provide the incidence rates of safety events of interest overall. If sample size allows, additional analysis in subgroups by gender and new users versus switcher from originator will be undertaken.

The general analytic approach will be descriptive and include rates of events of interest among Ruxience-treated patients. Data will be presented as number of events, incidence rates and 95 % confidence intervals. Such analyses will be performed by and at the direction of BSRBR based on an a priori statistical analysis plan (SAP) maintained by University of Manchester and shared with the Sponsor. The codes will be harmonised with other registers conducting similar analysis. A draft set of MedDRA codes is included in:

Index Date

The Index Date is the date of Ruxience initiation. Patients who switch from another therapy to Ruxience while they are enrolled in BSRBR-RA are eligible for enrollment, and the index date will be the date of Ruxience initiation.

Risk Window

Patients will be evaluated for safety events of interest while exposed to Ruxience and accrue person-time from Index Date until the first occurrence of the event of interest, death, date of last scheduled clinical data provision to the register, lost to follow up, exit from the register or completion of 3 years of follow up. The final report will censor all patients at 3 years after Date of Study Start. Follow up will be uniquely determined for each safety endpoint of interest.

Some outcomes of interest in this study are thought to potentially occur at a higher rate while on the drug, but that increased risk subsides after the drug is discontinued (ie, serious infections, CV events). In these situations, these events will be calculated using a risk window from Ruxience initiation until 270 days (eg, 9 months) after last infusion based on Ruxience's half-life and mechanism of action. This does not apply to patients who were lost to follow-up, have exited the registry, completed 3 years of follow-up or for whom the most recent date of clinical data provision to the register is within the 270 day window, in which case data will be censored on that date instead. Based on The National Institute for Care and Health Excellence (NICE) guidelines on the use of rituximab treatment, most patients will not be considered for further treatment with Ruxience until at least 6 months from the date of last infusion.

For non-melanoma skin cancer (NMSC) and other malignancies, the manifestation of which is expected to be delayed relative to the time of exposure, the outcomes will be evaluated from drug initiation until the first event, loss to follow up or completion of 3 years of follow up, reflecting a once exposed always at risk paradigm.

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9.8. Quality Control

BSRBR-RA have guidelines in place to monitor and maintain the quality of the data received. All information received on serious adverse events are reviewed by 1 of 2 trained registered nurses prior to coding. Reports can be sent from hospitals treating the patient, the patients themselves, or the national registers. Reporting malignancies to the national cancer registries is mandatory by law in the UK. To allow serious adverse events to be processed, the following information is required as a minimum:

- A legible and recognised disorder/sign/symptom;
- The date of event;
- Which targeted therapy drug(s) the patient was on at the time of the event.

Where information is missing, the BSRBR-RA pharmacovigilance team contacts the hospital to validate and confirm the details around the serious adverse event. Where a serious adverse event is patient reported, a request for information is sent to the hospital for validation. Events that do not fall under the definition of a serious adverse event are not subject to such validation. The data undergo regular validation checks both manually and automatically.

9.9. Limitations of the Research Methods

This study is designed to assess the safety of Ruxience within the clinical practice setting utilising the BSRBR-RA, a well-established UK based rheumatology register.

The RA treatment landscape has evolved over time with the introduction of new therapies, treatment recommendations, and approaches to managing these events. The rates of events of interest and their distribution among patient types may have changed over time.

Endpoint misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While the BSRBR-RA has an established system to identify and capture endpoint data, it is not feasible in such an observational study to verify all events via source documentation. It is also possible that some events will be missed as all reporting is done via the rheumatology departments. If rheumatologists are not aware of an event, they cannot report it and could result in underestimation of the incidence rate. For the serious events included in this analysis this is of low probability.

This study will continue for a period of 3 years after study start (assuming it is feasible to continue participation and that a sufficient number of Ruxience-treated patients can be enrolled). This period of time may not be sufficient to assess some events, particularly malignancies which may have a longer latency period. Another limitation is the absence of a control group which does not allow for the comparison of incidence rates among Ruxience exposed patients to patients exposed to other treatments. Conclusions may not be generalisable outside of the 3 year period since initiation of therapy.

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9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

This study involves data that exist in anonymised structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves anonymised structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required. The University of Manchester will obtain written informed consent from all patients prior to data collection.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

The analyses for the Ruxience PASS will be completed using fully anonymised data. The data will not contain any patient identification information (eg, name), except for a unique number assigned for the purpose of linking files.

The BSRBR-RA protocols are approved by the North West 5 Research Ethics Committee (REC 00/8/053 with most recent approval amendment (#27) approval date of 06 Dec 2018).

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), EMA, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology. See ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

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In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

Annual reports will be prepared by BSRBR and shared with Pfizer. Analysis using linked register data through 3 years of follow up will be the basis for the study final report. Data may be used in regulatory communications external to the UK or for contextualisation purposes. Manuscripts based on specific endpoints of interest may be developed for publication purposes.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol of which the investigator becomes aware.

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14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable.

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ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Table 2. ICD and MedDRA Codes for Select Safety Endpoints

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	**Operationalisation**	**Validation ICD**	**Operationalisation (Final list TBD based on reported endpoints)**
Serious infections	Hospitalisations in the Patient Register listing as main diagnosis ICD10-codes below. If main diagnosis is RA, contributory diagnoses are also considered. A00-B99 (excluding A33 and A50), D73.3, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J39.0-J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00-L08, L30.3, M00-M01, M46.2-M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N13.6, N15.1, N15.9, N30.0 N30.8, N34.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1.	This algorithm has not been specifically validated in ARTIS, but the register itself is subject to strict quality assurance routines and has been validated several times. References: Ludvigsson et al. External Review and Validation of the Swedish National Inpatient Register, BMC Public Health, 2011 (11):450. http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish.	Hospitalisation and/or use of parenteral antibiotics + MedDRA Infections and Infestations SOC 10021881.
CV risk	Major Acute Cardiovascular Events (MACE), combines MI, stroke, and fatal cardiovascular events: I00-I99 as main cause of death, or I20.0, I21, I60-I64 as diagnosis in in- or outpatient care.	See Serious Infections 'Outcome' was defined as any first-ever acute coronary syndrome (ACS) event, which in turn was defined as a primary discharge diagnosis of acute myocardial infarction or unstable angina pectoris, or as acute myocardial infarction being the underlying cause of death. For discharge diagnoses, the date of admission to hospital was considered the event date. This outcome definition has	Fatal and non-fatal 10000891 Acute myocardial infarction; 10006147Brain stem infarction; 10006148 Brain stem ischaemia; 10008034 Cerebellar infarction; 10008088 Cerebral artery embolism; 10008120 Cerebral ischaemia; 10008190 Cerebrovascular accident; 10014498 Embolic stroke; 10019005 Haemorrhagic cerebral infarction; 10019016 Haemorrhagic stroke; 10024033 Lateral medullary syndrome; 10028596 Myocardial infarction; 10028602 Myocardial necrosis; 10033697 Papillary muscle infarction; 10043647 Thrombotic stroke; 10049768 Silent myocardial infarction; 10051078 Lacunar infarction; 10055677 Haemorrhagic

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Table 2. ICD and MedDRA Codes for Select Safety Endpoints

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	**Operationalisation**	**Validation ICD**	**Operationalisation (Final list TBD based on reported endpoints)**
		previously been validated in a Swedish early RA cohort, with a positive predictive value of 95%. In addition, a regional validation study of hospitalised acute MI and stroke found positive predictive values of 96% and 94% respectively, in the period 1977 to 1987. References: https://onlinelibrary.wiley.com/doi/epdf/10.1002/art.39267 Mantel et al. Risk Factors for the Rapid Increase in Risk of Acute Coronary Events in Patients With New-Onset Rheumatoid Arthritis. A Nested Case-Control Study. Arthritis & Rheumatology. 2015; 67(11):2845-2854. Lindblad et al. Validity of register data on acute myocardial infarction and acute stroke. Scandinavian Journal of Public health 1993; 21 (1):3-9.	transformation stroke; 10056237 Migrainous infarction; 10059613 Stroke in evolution; 10060839 Embolic cerebral infarction; 10060840 Ischaemic cerebral infarction; 10061256 Ischaemic stroke; 10062573 Brain stem thrombosis; 10064961 Thalamic infarction; 10066591 Post procedural stroke; 10066592 Post procedural myocardial infarction; 10067167 Cerebellar embolism; 10067347 Thrombotic cerebral infarction; 10067462 Millard-Gubler syndrome; 10068621 Cerebellar ischaemia; 10068644 Brain stem stroke; 10069020 Basal ganglia infarction; 10070671 Cerebral septic infarct; 10070754 Inner ear infarction; 10071043 Basal ganglia stroke; 10071260 Carotid angioplasty; 10073945 Perinatal stroke; 10074422 Brain stem embolism. Fatal only 10002886 Aortic aneurysm rupture; 10003173 Arterial rupture; 10003210 Arteriosclerosis; 10003212 Arteriosclerosis moenckeberg-type; 10006145 Brain stem haemorrhage; 10007522 Cardiac asthma; 10007554 Cardiac failure; 10007556 Cardiac failure acute; 10007558 Cardiac failure chronic; 10007559 Cardiac failure congestive; 10007559 Cardiac failure congestive; 10007560 Cardiac failure high output; 10007625 Cardiogenic shock; 10007684 Carotid arterial embolus; 10007686 Carotid artery aneurysm; 10007688 Carotid artery thrombosis; 10008023 Cerebellar artery thrombosis; 10008030 Cerebellar haemorrhage; 10008076 Cerebral aneurysm ruptured syphilitic; 10008086 Cerebral arteriovenous malformation haemorrhagic;

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Table 2. ICD and MedDRA Codes for Select Safety Endpoints

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	**Operationalisation**	**Validation ICD**	**Operationalisation (Final list TBD based on reported endpoints)**
			10008089 Cerebral artery occlusion; 10008092 Cerebral artery thrombosis; 10008111 Cerebral haemorrhage; 10008118 Cerebral infarction; 10008132 Cerebral thrombosis; 10018985 Haemorrhage intracranial; 10022758 Intracranial aneurysm; 10022840 Intraventricular haemorrhage; 10022841 Intraventricular haemorrhage neonatal; 10024119 Left ventricular failure; 10024242 Leriche syndrome; 10034476 Pericardial haemorrhage; 10036511 Precerebral artery occlusion; 10039163 Right ventricular failure; 10039330 Ruptured cerebral aneurysm; 10042316 Subarachnoid haemorrhage; 10042434 Sudden death; 10047279 Ventricle rupture; 10048380 Aneurysm ruptured; 10048761 Atrial rupture; 10049418 Sudden cardiac death; 10049993 Cardiac death; 10050403 Carotid artery dissection; 10051093 Cardiopulmonary failure; 10051328 Carotid aneurysm rupture; 10052019 Femoral artery occlusion; 10053633 Cerebellar artery occlusion; 10053649 Vascular rupture; 10053949 Vascular pseudoaneurysm ruptured; 10055803 Haemorrhage coronary artery; 10058178 Aortic occlusion; 10060874 Aortic rupture; 10060953 Ventricular failure; 10060964 Arterial haemorrhage; 10062585 Peripheral arterial occlusive disease; 10062599 Arterial occlusive disease; 10063081 Acute left ventricular failure; 10063082 Acute right ventricular failure ; 10063083 Chronic left ventricular failure; 10063084 Chronic right ventricular failure; 10064595 Haemorrhagic arteriovenous malformation; 10064601 Iliac artery occlusion; 10065441 Venous haemorrhage; 10065558 Aortic

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Table 2. ICD and MedDRA Codes for Select Safety Endpoints

	ARTIS		BIOBADASER, BSRBR, RABBIT
Event	**Operationalisation**	**Validation ICD**	**Operationalisation (Final list TBD based on reported endpoints)**
			arteriosclerosis; 10067057 Basal ganglia haemorrhage; 10067116 Carotid arteriosclerosis; 10068119 Aortic dissection rupture; 10068119 Aortic dissection rupture; 10068230 Cardiorenal syndrome; 10069694 Brachiocephalic artery occlusion; 10069695 Subclavian artery occlusion; 10069696 Coeliac artery occlusion;10071716 Vertebral artery dissection; 10072043 Central nervous system haemorrhage; 10072789 Iliac artery rupture; 10073565 Intracranial artery dissection; 10073565 Intracranial artery dissection; 10073681 Epidural haemorrhage; 10075449 Brachiocephalic arteriosclerosis; 10076203 Radiation associated cardiac failure.
NMSC	Identified through the Cancer register as all malignancies with ICD-O/2 code C44, and all basal cell cancers recoded in the register's subcomponent on basal cell cancers Alt: all invasive NMSC, identified as non-benign ICD-O/2 code C44, and no basal cell cancers.	About 99% of cancers have been morphologically verified. Reporting of incident cancers (including invasive malignancies as well as cancer in situ) is mandatory and semi automated, resulting in an estimated coverage greater than 95%.	10004146 Basal cell carcinoma; 10004178 Basosquamous carcinoma; 10004179 Basosquamous carcinoma of skin; 10006059 Bowen's disease; 10007390 Carcinoma in situ of skin; 10064055 Lip squamous cell carcinoma; 10063693 Malignant neoplasm of eyelid; 10040808 Skin cancer; 10055115 Skin cancer metastatic 10041834 Squamous cell carcinoma of skin.
Malignancy	All invasive malignancies recorded in the cancer register, excluding NMSC.	See NMSC.	Malignant or unspecified tumours (SMQ).

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

bDoc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: An Active Surveillance, Post Authorization Safety Study (PASS) of Serious Infection, Malignancy, Cardiovascular (CV) and Other Safety Events of Interest among Patients Treated with Ruxience for Moderately to Severely Active Rheumatoid Arthritis (RA) within the British Society for Rheumatology Biologics Register Rheumatoid Arthritis (BSRBR RA).

EU PAS Register® number:
Study reference number (if applicable):B3281011

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	N/A
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

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Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8, 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	N/A
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	N/A

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.4
4.2.2 Age and sex	☐	☐	☒	N/A

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Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.4
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2.1-9.6
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.2.1-9.6
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.2.1-9.6
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.2.1-9.6
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.2.1-9.6
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	N/A

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.5.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Appendix 1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	N/A
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	N/A

Comments:

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Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	N/A
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	N/A
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	N/A

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protbocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	N/A

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	N/A
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.6
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.6
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.6
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.6
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.6
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	N/A
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.5.2 and Appendix 1
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	N/A

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Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.9
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	N/A
10.3 Are descriptive analyses included?	☒	☐	☐	
10.4 Are stratified analyses included?	☐	☐	☒	N/A
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	N/A
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	N/A
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	N/A
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	N/A

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.10
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	N/A
12.1.2 Information bias?	☒	☐	☐	9.11
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	N/A
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	N/A

Comments:

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Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.4
13.3 Have data protection requirements been described?	☒	☐	☐	10.1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Cynthia de Luise

Date: 25 Sept 2020

Signature: 

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ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

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